Pergamon

Tetrahedron, Vol. 53, No. 22, pp. 7397-7402, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)00425-0

Anomalous Horner-Wadsworth-Emmons Reactions on 3,4-Enuloses.

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Abstract: Pyranosic enuloses were subjected to Horner-Wadsworth-Emmons (HWE) conditions using the enolate of dimethyl(methoxycarbonyl)methyl phosphonate and its ethyl analogue. 3-O-Phosphorylation of the products as well as an unusual stereoespecificity were observed. A mechanism involving a phosphonate-phosphate like rearrangement through a five member intermediate followed by benzoate elimination is proposed. © 1997 Elsevier Science Ltd.

INTRODUCTION

Cyclic ketones have been widely used for the introduction of a chain appendix to a cycle through olefination reactions. In the carbohydrate field, it is well known the utility of uloses as substrates for the synthesis of branched chain sugars.[1 a,b]

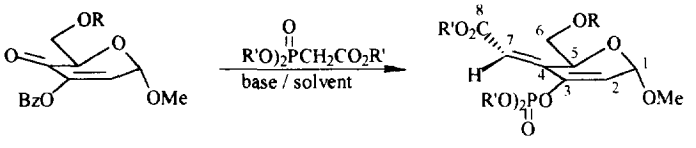
In previous work,[2] we prepared methyl 3,6-di-*O*-benzoyl-2-deoxy-α-D-*glycero*-hex-2-enopyranosid-4-ulose (**1**) and its silylated analog methyl 3-*O*-benzoyl-6-*O*-(*tert*-butyldiphenyl)silyl-2-deoxy-α-D-*glycero*-hex-2-enopyranosid-4-ulose (**2**) starting from D-galactose as key intermediates for the synthesis of thromboxane like structuctures[3 a,b] The introduction of a chain appendix on C-4 was required as the next step in our synthetic pathway. Although olefination reactions have been performed on α-β unsaturated ketones, as far as we know, this kind of reactions has not been tried on enuloses. Nevertheless, we decided to try compounds **1** and **2** as precursors since a retrosynthetic analysis showed that the introduction of the required chain appendix through olefination on the enuloses followed by hydrogenation could be advantageous.

HWE conditions were preferred over Wittig conditions because of the advantages that the use of phosphonates presents when labile compounds are employed.[4] Moreover, when enuloses **1** and **2** were subjected to Wittig conditions, pyrones were obtained as a result of the strong alkaline conditions required.

In this paper we describe the anomalous results obtained when compounds **1** and **2** were subjected to HWE conditions yielding 3-O-phosphorylated products. We suggest a mechanism that could explain the results.

RESULTS AND DISCUSSION

A solution of methyl 3,6-di-*O*-benzoyl-2-deoxy-α-D-*glycero*-hex-2-enopyranosid-4-ulose (**1**) in toluene was treated with an excess of the potassium enolate of dimethyl(methoxycarbonyl)methyl phosphonate. After 30 min no starting material was detected by tlc. Column chromatography afforded a single product that was characterized as methyl 6-*O*-benzoyl-2,4-dideoxy-4-C-[*E*(methoxy carbonyl)methylene]-3-*O*-dimethoxyphos-phoryl-α-D-*glycero*-hex-2-enopyranoside (**3**) (Scheme 1).



1 R = Bz
2 R = TBDPS

Scheme 1

3 R = Bz; R' = Me
4 R = TBDPS; R' = Me
5 R = Bz; R' = Et
6 R = TBDPS; R' = Et

^{1}H and ^{13}C-NMR spectra were completely assigned using bidimentional homo and heteronuclear correlation experiments. The ^{1}H-NMR spectrum of **3** (Table 1) showed two singlets at 6.20 and 6.16 ppm corresponding to two olefinic protons and a singlet at 3.75 ppm corresponding to a new methoxyl group indicating that olefination had taken place. A multiplet corresponding to five aromatic protons was observed at lower fields. Two intense doublets at 3.77 and 3.83 ppm, which integrated for three protons each with a coupling constant of 1.4 Hz were observed. These signals could be assigned to two methoxyl groups from a phosphoric ester, the protons being coupled through three bonds with the ^{31}P nucleus, in accord with literature references.[5,6] These observations indicated that a phosphate group was substituting C-3 instead of a benzoate group.

The ^{13}C-NMR spectrum (Table 2) showed only two signals for carbonyl groups, which belonged to the existing benzoyl group and to the methoxycarbonyl group incorporated. There were no signals corresponding to ketone carbonyls, and two new signals corresponding to the expected exocyclic olefinic bond were observed (141.0 ppm and 116.9 ppm for C-4 and C-7 respectively). The signals for C-2 (113.9 ppm), C-3 (142.0 ppm) and C-4 appeared as doublets with coupling constants of 3.0, 7.8 and 5.7 Hz due to the coupling through two and three bonds with the phosphorous atom in accord with literature data.[7]

When the reaction was performed over the sililated analog methyl 3-*O*-benzoyl-6-*O*-(*tert*-butyldiphenyl)silyl-2-deoxy-α-D-*glycero*-hex-2-enopyranosid-4-ulose (**2**), methyl 6-*O*-(*tert*-butyldiphenyl)silyl -2,4-dideoxy-4-C-[*E*(methoxycarbonyl)methylene]-3-*O*-dimethoxyphosphoryl-α-D-*glycero*-hex-2-enopyranosi de (**4**) was obtained. (Tables 1 and 2). The reaction of enuloses **1** and **2** with the enolate of diethyl (ethoxycarbonyl)methyl phosphonate, yielded methyl 6-*O*-benzoyl-2,4-dideoxy-4-C-[*E*(ethoxycarbonyl) methylene]-3-*O*-diethoxyphosphoryl-α-D-*glycero*-hex-2-enopyranoside (**5**) and methyl 6-*O*-(*tert*-butyl diphenyl)silyl-2,4-dideoxy-4-C-[*E*(ethoxycarbonyl)methylene]-3-*O*-diethoxyphosphoryl-α-D-*glycero*-hex-2-enopyranoside (**6**) (Tables 1 and 2).

The fact that no Nuclear Overhauser Effect between H-7 and H 6,6′ and H-5 was observed in the NOESY spectra may suggest that the mentioned protons lay far apart from each other,but, since only one

diasteromer was obtained, no definite conclusion regarding on the stereochemistry could be made based on this experiment.

Table 1. ^{1}H-NMR Data for Compounds **3 - 6**.

Compound	H-1	H-2	H-5	H-6	H-6'	H-7	OCH_3 (C-1)
3	6.34	6.16	4.86	4.53		6.20	3.58
4	6.27	6.12	4.58	3.76		6.27	3.54
5[a]	6.34	6.16	4.87	4.47	4.53	6.21	3.58
6[b]	6.28	6.12	4.58	3.71	3.85	6.26	3.53

[a]yield 84%, $[\alpha]_D$ +34.1° (c 0.46, $CHCl_3$), Analysis: calculated for $C_{22}H_{29}O_{10}P$ %C = 54.55, %H = 6.03; found %C = 54.97, %H = 6.31. [b]yield 57%,$[\alpha]^{20}_D$ = +12.6° (c 0.68, $CHCl_3$). Analysis: calculated for $C_{31}H_{43}O_9PSi$ %C = 60.18, %H = 7.00; found %C = 60.39, %H =7.28.

Table 2. ^{13}C-NMR Data for Compounds **1 - 6**.

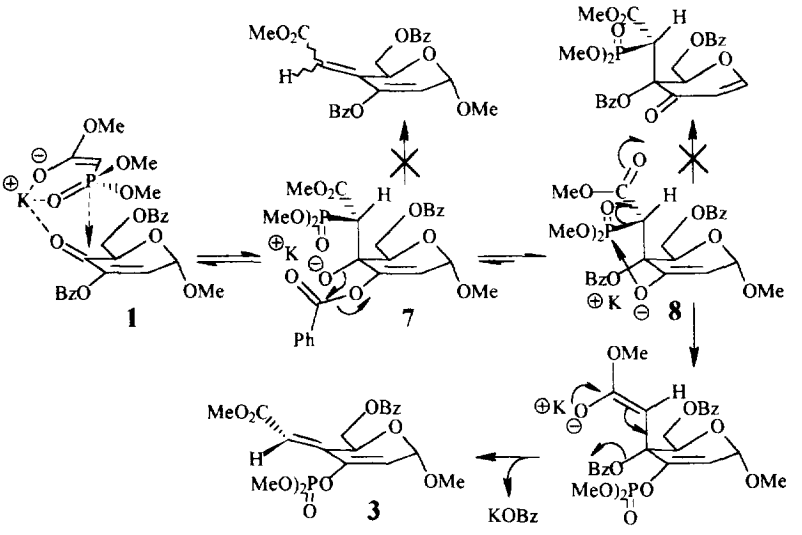
Compound	C-1	C-2 ($^3J_{P,C}$)	C-3 ($^2J_{P,C}$)	C-4 ($^3J_{P,C}$)	C-5	C-6	C-7 ($^4J_{P,C}$)	C-8	OCH_3 (C-1)
1	95.2	128.4	147.3	187.9	73.5	62.9			56.8
2	95.1	129.9	144.3	188.2	76.6	63.1			56.4
3[a]	95.3 ($^1J_{P,C}$ 3.4)	113.9 (3.0)	142.0 (7.8)	141.0 (5.7)	66.1	65.6	117.0	166.2	56.2
4[b]	95.1	113.1	141.3	141.0	68.3	65.6	118.4 (3.8)	165.5	56.0
5[c]	95.3	114.5	142.1 (6.9)	140.5 (6.9)	66.0	65.7	116.4 (3.0)	166.2	56.1
6[d]	95.1	113.7	141.5	141.3 (1.8)	68.2	65.7	118.1 (2.7)	165.3	55.9

[a]$CH_3O)_2PO_2$: 55.1, CH_3OCO: 51.6; [b]$CH_3O)_2PO_2$: 54.9, 55.2; CH_3OCO: 51.6. [c]$CH_3CH_2O)_2PO_2$: 15.9, 16.1 and 64.8, 64.9; CH_3CH_2OCO: 14.1, 60.6; ^{31}P-NMR: - 6.0 (s, $CH_3CH_2O)_2PO_2$).. [d]$CH_3CH_2O)_2PO_2$: 15.9, 16.1 and 64.7, 64.8; CH_3CH_2OCO: 14.2, 60.5.

A comparison of the values for the shifts of the signals in ^{13}C-NMR spectrum for compounds **3** and **4** and its precursors **1** and **2** showed that C-6 in **3** and **4** appears 2.6 ppm downfield from the corresponding signals in **1** and **2** (Table 3). This deshielding effect would be operating if the methoxycarbonyl group introduced lays near enough to C-6 as would be the case of the *E* isomer. This influence was already observed by Hanessian[3a] for methyl 3-*O*-benzoyl-6-*O*-(*tert*-butyldiphenyl)silyl-2,4-dideoxy-4-C-[*E*(methoxycarbonyl) methylene]-α-D-*erythro*-hexopyranoside, which showed the signal of its C-6 deshielded 2.6 ppm with respect to the corresponding signal in its ulose precursor; while in the *Z* isomer no shift was observed. These observations lead us to propose an *E*-stereochemistry around the exocyclic double bond. No further attempts were made to prove the stereochemistry of this olefin because *E* and *Z* geometries were equally useful for our synthetic purposes.

The most remarkable features of this process were the phosphorylation of the enolic oxygen at C-3; and the uncommon stereospecificity observed, taking into account that this reaction is not usually stereoselective when is performed on cyclic ketones (even when it is so with aldehydes[8,9]).

The formation of compounds **3-6** could not be explained through the normal mechanism described for HWE reactions. If we assume that the nucleophilic attack occurs axially from the less hindered face of the molecule, an oxi-anion intermediate **7** (scheme 2) would be formed in a similar way as that proposed for the mechanism of reactions with phosphoranes.[10] In this intermediate the oxi-anion adopts an equatorial orientation favouring a benzoyl migration from the adjacent carbon to give enolate **8**, which is more stable than **7** because of the better dispersion of negative charge. This step can be followed by a phosphonate-phosphate like rearrangement.[11] In our case, the irreversible phosphorylation step would take place through a five member cyclic intermediate involving the enolic oxi-anion at C-3. This kind of intermediate is the most stable in intramolecular nucleophilic substitution reactions on the phosphorous atom[12] and is energetically favoured compared with the four member intermediate through which the "normal" product would be obtained.[13-15] Moreover, this irreversible phosphorylation step would avoid β-elimination of the anomeric methoxy group, which was not observed even when such systems show a strong tendency to direct elimination of methanol.[16] As far as we know, this is the first evidence of such rearrangements through five member intermediates in HWE reactions.

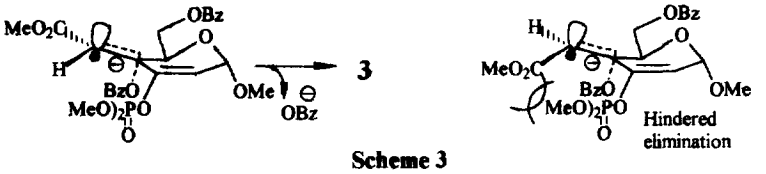


Scheme 2

Stereoelectronic effects can be ruled out from the causes of the sterospecificity of the reaction because even when an oxygenated subtituent on α or β respect to the carbonyl group has influences on the stereospecificity of the olefination reactions,[17,18] in our case, both carbons α to carbonyl bear oxygenated substituents and it is not likely that the driving effect of one of them should predominate over the other, so, we can't attribute the observed stereoselectivity to that effect. As the same product was obtained when the reaction was carried at -78°C a base catalysed isomerization was also discarded because it requires much more energetic conditions.[19]

Even when a concerted elimination of benzoate may yield the obtained olefin, the lack of the required coplanarity of the four centres involved[20] made us rule out that possibility. Therefore, a mechanism analogous to E1cB, where the formation of the anionic intermediate is a fast and irreversible step, is proposed. The

observed stereochemistry should be a consequence of the steric requirements during the formation of the π bond. With these requirements, *Z* isomer would not be formed because of the severe 1,3-allylic interactions in the respective transition state (scheme 3).



Scheme 3

Anomalous results of the Horner-Wadsworth-Emmons reaction have been reported before.[21,22] but no attempt has been made to explain the uncommon behaviour observed. The postulated intramolecular phosphorylation-elimination sequence may contribute to their explanation.

This is the first report of the use of enuloses as substrates for HWE reactions. Although olefination didn't yield the expected products, the results here described are of synthetic interest since the compounds obtained bear a phosphate at C-3 and have a definite stereochemistry.

EXPERIMENTAL

General Remarks

All air and moisture sensitive reactions were carried out under nitrogen using oven-dried glassware. Dimethyl(methoxycarbonyl)methyl phosphonate and diethyl(ethoxycarbonyl)methyl phosphonate, were used as supplied commercially. Column chromatography was performed on silicagel 60. TLC was carried out on precoated aluminum plates (0.1 mm) of silicagel 60 F-254; detection was effected by exposure to UV light and by spraying the plates with 5 % (v/v) H_2SO_4 in ethanol followed by heating. ^{1}H-NMR spectra were recorded at 200.13 MHz in $CDCl_3$. ^{13}C-NMR spectra were recorded at 50.13 MHz in $CDCl_3$. Chemical shifts are given in ppm from TMS. ^{31}P-NMR spectra was recorded at 121.5 MHz in $CDCl_3$. Chemical shift is given in ppm from H_3PO_4 85 %. IR spectra were performed with a FT-spectrometer.

Methyl 6-*O*-benzoyl-2,4-dideoxy-4-C-[*E*(methoxycarbonyl)methylene]-3-*O*-dimethoxyphosphoryl-α-D-*glycero*-hex-2-enopyranoside (3).

0.307 g (0.802 mmol) of enulose **1** in toluene (6.0 mL) were treated with 5.0 mL of a 0.2 M solution of the potassium enolate of dimethyl(methoxycarbonyl)methyl phosphonate prepared from 0.37 mL (2.24 mmol) of dimethyl(methoxycarbonyl)methyl phosphonate and 1.0 mL of a 1.0 M solution of KOtBu in tetrahydrofuran. After 30 min the reaction mixture was poured over 120 mL of ethyl acetate, and washed with saturated $NaHCO_3$, NaH_2PO_4 (10 %) and NaCl (10 %). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to give, after column chromatography, 0,632 mg (65 %) of a homogeneous syrup that was characterized as compound **3**.

$[\alpha]^{20}_D$ = + 38.6° (c 0.56, $CHCl_3$). Analysis: calculated for $C_{19}H_{23}O_{10}P$ %C = 51.59, %H = 5.24; found %C = 52.00, %H = 5.63. IR (NaCl) ν_{max} (cm^{-1}) : 1728 (C=O, methoxycarbonyl); 1719 (C=O, benzoate); 1280 (P=O). ^{1}H and ^{13}C-NMR see Tables 1 and 2.

Methyl 6-*O*-(*tert*-butyldiphenyl)silyl-2,4-dideoxy-4-C-[*E*(methoxycarbonyl)methylene]-3-*O*-dimethoxy phosphoryl-α-D-*glycero*-hex-2-enopyranoside (4).

Compound **4** was obtained from compound **2** in 67 % yield in a similar way as that described for the preparation of compound **3**. $[\alpha]^{20}_{D}$ = + 14.8° (c 1.13, $CHCl_3$). Analysis: calculated for $C_{28}H_{37}O_9PSi$ %C = 58.32, %H = 6.47; found %C = 58.61, %H = 6.05. IR (NaCl) ν_{max} (cm^{-1}) : 1735 (C=O, methoxycarbonyl); 1290 (P=O). ^1H and ^{13}C-NMR see Tables 1 and 2.

Aknowledgements.

We wish to thank Universidad de Buenos Aires and Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET) for financial support and UMYMFOR for the microanalyses. A. Fernández Cirelli is a Research Fellow in CONICET.

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(*Received in USA* 26 *February* 1997; *accepted* 8 *April* 1997)